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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/626,879

07/25/2003

Jang Han

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NOVARTIS VACCINES AND DIAGNOSTICS INC.

INTELLECTUAL PROPERTY- X100B

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EXAMINER

ZARA, JANE J

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

10/07/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/626,879	Applicant(s) HAN ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-7,14,15,17-20,24,25,43,45-56,67-74,81,84,87 and 89-91 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>Seq Alignment Data</u> |

DETAILED ACTION

This Office action is in response to the communication filed 6-5-09.

Claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wands et al (USPN 6,001,990, Cha et al (USPN 6,297,370), Rice et al (USPN 6,297,003), the combination in view of Fire et al (USPN 6,506,559), the combination further in view of Fosnaugh et al (US 2003/0143732), Morrissey et al (US 2003/0206887) and McKay et al (USPN 6,133,246), and Alsobrook et al (US 2003/0219823) for the reasons of record set forth in the Office action mailed 12-9-08.

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The claims are drawn to methods of inactivating, inhibiting and/or treating hepatitis C virus (HCV) comprising administration of siRNA sharing at least 95% or 97% identity to SEQ ID NOs. 1, or 10-28, which target and inhibit nucleic acids encoding HCV, and which siRNA further comprise 2'-fluoro or 2'-O-methyl modified groups, a modified cytosine, which siRNA are optionally expressed via an expression vector, and which siRNA are operatively linked to a first and second promoter, comprising a U6 and H1 promoter, and which siRNA optionally further comprise modified internucleotide linkages.

Wands et al (USPN 6,001,990) teach the inhibition of HCV RNA translation comprising the administration of antisense oligonucleotides that specifically target nucleic acids encoding HCV, and which antisense comprise at least 95% or 97% identity with SEQ ID NOs. 10 and 10-28 (See esp. the abstract, col. 1-8, 10-17; SEQ ID NO. 2, 3, 12, and 30).

Cha et al (USPN 6,297,370) teach antisense oligonucleotides for inhibiting the transcription and translation of HCV, and which share at least 95% or 97% identity with SEQ ID NO. 1 or 10-28 (See esp. col. 1-4; claims 1-6, 10, 11; SEQ ID No. 120).

Rice et al (USPN 6,297,003) teach antisense oligonucleotides for inhibiting the expression of HCV, and which share at least 80% identity with SEQ ID NO. 1 or 10-28 (See esp. the abstract, col. 1-3, 8-10, 18, 22; SEQ ID NO. 34).

The primary references of Wands, Cha and Rice do not teach siRNA molecules for inhibiting HCV infections, nor all of the modifications instantly claimed, nor the use of U6 and H1 promoters to drive expression of siRNA in an appropriate expression vector.

Fire et al (USPN 6,506,559) teach the use of inhibitory oligonucleotides in inhibiting the expression of target genes in vitro and in vivo. Fire teaches the advantages of using siRNA for target gene inhibition compared to other inhibitory oligonucleotides, including antisense and ribozymes, and teaches the use of expression vectors for expressing siRNA molecules in an organism. Fire also teaches the incorporation of modified internucleotide linkages and modified nucleotides into siRNA molecules for enhancing oligonucleotide stability, target binding and cellular uptake (see the abstract; col. 1-5, 7; claims 1-6, 10, 21).

Alsobrook et al (US 2003/0219823) teach expression vectors comprising U6 or H1 for expression of siRNA in an appropriate target cell (see esp. paragraph 0090).

Fosnaugh et al (US 2003/0143732) teach various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh et al also teach compositions comprising modified and unmodified siRNAs and RISC for target gene inhibition see p. 1, 3-4, 6-9, p. 16 and figures 4 and 5, claim 30).

Morrissey et al (US 2003/0206887) teach various ways of designing and optimizing 2'- modifications on siRNA, including 2'-fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'substitutents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

McKay et al (USPN 6,133,246) teach numerous motifs and combinations of modified residues within antisense oligonucleotides, including the incorporation of 2'- modified sugars which include 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, modified nucleobases including modified cytosines, modified internucleotide linkages, 2'- β -D-deoxynucleosides and combinations thereof, as well as the optimization of modifications for maximizing target binding, cellular uptake and oligonucleotide stability (see esp. col. 7-12; Tables 4-26, esp. Tables 11 and 12, and Table 26).

It would have been obvious to design and utilize siRNA molecules that share at least 80% identity with SEQ ID NOs. 1, 10-28 for inhibiting HCV replication and HCV infection because antisense oligonucleotides comprising this sequence identity were well known in the art at the time the instant invention was made, as illustrated by the teachings of Wands, Cha and Rice, and siRNA molecules were well known in the art to target and inhibit a target gene of known sequence more efficiently than antisense or ribozymes, as taught previously by Fire. One would have been motivated to utilize siRNA molecules comprising SEQ ID Nos. 1, or 10-28 because these target regions of

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the HCV were well known to be accessible to antisense oligonucleotides, and siRNA were known to be more effective inhibitors of target gene expression. One would have been motivated to inhibit the expression or replication of HCV because HCV infections are known to cause deleterious effects in humans, as taught previously by many in the art, including Wands, Cha and Rice. One of ordinary skill would have reasonably expected to utilize the antisense oligonucleotides previously taught and tested by Wands, Cha and Rice in siRNA constructs and achieve target gene inhibition because of the known advantages of siRNA, as taught previously by Fire et al, and the accessibility of these regions of HCV were also well known in the art, as previously disclosed by Wands, Cha and Rice.

One of ordinary skill in the art would have been motivated to express siRNA molecules, either as a single, self-complementary molecule, or as two separate strands, because expression of siRNA within a cell from an appropriate expression vector provides increased siRNA within a target cell. One of ordinary skill in the art would have been motivated to use the well known and reliable U6 and H1 promoters to drive expression in an appropriate expression vector because these promoters are well known in the art to provide for predictable and high expression of siRNA in a target cell, as taught previously by AlsoBrook et al.

It would have been obvious to incorporate 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate

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internucleotide linkages, and which oligonucleotides optionally further comprise modified nucleobases, including modified cytosines into siRNA molecules for enhancing their target binding and stability, yet minimizing inactivation of the siRNA ability to inhibit target gene expression because Fosnaugh, Morrissey, Fire and McKay all teach the advantages of incorporating these modifications into inhibitory oligonucleotides for enhancing target gene binding, cellular uptake and oligonucleotide stability. One of ordinary skill would have expected that the incorporation of these modifications are optimized using routine experimentation, and one of ordinary skill in the art would have expected that the siRNA molecules, modified as instantly claimed, would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA. One of ordinary skill in the art would have reasonably expected that these modifications would provide for the advantages previously taught, of enhancing target binding and oligonucleotide stability, and would lead to improved target gene inhibition.

Applicant's arguments filed 6-5-09 have been fully considered but they are not persuasive. Applicant argues that the instant invention is not obvious because the mere identification of an inhibitory antisense transcript, without more, provides little by way of predicting the behavior of the same transcript in siRNA-targeted gene inhibition. Applicant argues that the present application fails to meet a minimum threshold of at least some degree of predictability required for a determination of obviousness.

Contrary to Applicant's assertions, the prior art is rich in teachings concerning the accessibility of HCV target gene(s) to numerous antisense that target the identical

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regions of the target gene as instantly claimed. And, while a different mechanism of target gene inhibition is utilized for siRNA (e.g. involving RISC), the previous disclosure of the myriad of antisense that are now contained within newly minted versions of inhibitory oligonucleotide molecules, combined with the routine experimentation required to test identical antisense target sequences now embraced within siRNA molecules, renders the instant invention obvious.

The prior art teaches many antisense sequences that share 100% identity with instantly claimed sequences, e.g. SEQ ID NOs. 1, 10, 11, 28 of the instant application (see accompanying sequence alignment data). Using the technology well known in the art to synthesize siRNA, and using the technology well known in the art to test target gene inhibition by siRNA, one would have reasonably expected that the instantly claimed siRNA molecules would successfully inhibit HCV gene expression..

For these reasons, the instant rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

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you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
10-6-09

/Jane Zara/

Primary Examiner, Art Unit 1635